

The simulation of the activity dependent neural network growth

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It is currently accepted that cortical maps are dynamic constructions that are altered in response to external input. Experience-dependent structural changes in cortical microcircuits lead to changes of activity, i.e. to changes in information encoded. Specific patterns of external stimulation can lead to creation of new synaptic connections between neurons. The calcium influxes controlled by neuronal activity regulate the processes of neurotrophic factors released by neurons, growth cones movement and synapse differentiation in developing neural systems. We propose a model for description and investigation of the activity dependent development of neural networks. The dynamics of the network parameters (activity, diffusion of axon guidance chemicals, growth cone position) is described by a closed set of differential equations. The model presented here describes the development of neural networks under the assumption of activity dependent axon guidance molecules. Numerical simulation shows that morpholess neurons compromise the development of cortical connectivity.

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I. INTRODUCTION

Neural networks are not constant structures. Modification in neural nets leads to changes in mapping of input signal to output. The most explored type of neural plasticity is synaptic plasticity. Synaptic plasticity deals with modifications of connection strength between neurons. It is an activity dependent process, and synaptic efficacy modifications depend on activity of postsynaptic and presynaptic neurons [1, 2]. The second type of plasticity is known as structural plasticity. Structural plasticity deals with anatomical structure of neurons, and connections between neurons. The anatomical structures of neurons are subject to variation, and new connections between neurons can be established or deleted [3] in the course of development of neuron net. Structural plasticity as well as synaptic plasticity is a permanent and activity dependent process. Because it is an activity dependent process it can be the basis of learning. Activity-dependent modifications of neural circuits lead to changes in activity pattern of whole network. The geometrical properties of neurons should be considered in the theoretical investigations of structural plasticity of neural networks. The network must be considered as a system of neurons in three dimensional neuropil where neurons communicate with each other. The geometrical properties of neurons and the neuropil where neurons are constituent elements of networks. The neural networks generate activity patterns which depend on the intrinsic state of individual neuron and external influences on the system. This activity influences structural plasticity process. An external signal changes the activity pattern and leads to creation of new connections i.e. network will be modified according to external information.

The neurons without connections can be considered a system of neurons in three dimensional space. At the beginning, the neurons interact only by emission of chemicals. Even no connections between neurons exist it may still be considered a system. With time new connections between neurons appear and the system will possess' new properties and neurons can make influence on the activity of each other neurons.

In vivo and in vitro neurons self-organize into networks [4, 5]. Mature networks can be considered a result of activity-dependent dynamical wiring process. Single neurons have properties that form the assembly into networks. Calcium plays the most important role in wiring process [6, 7, 8]. Neuronal activity via voltage-dependent calcium channels provide influx of calcium through membrane. Intracellular calcium activates and regulates different intercellular processes which influences growth cone movement, axon elongation, neurotrophin release, synaptogenesis, among other molecular mechanisms. The molecular mechanisms of most of these processes remains unclear and are subjects of many experimental studies. Wiring process is controlled by intrinsic neuronal activity and neural activity is caused by sensory experience (external signals). External signals regulate neuronal activity and leads formation of the wiring between neurons. This adaptation leads to different neural activity even under constant sensory input, enabling the building of more complex representation and leading to progressive cognitive development.

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Three levels of neuronal response to external signals can be considered: (i) induced spikes, (ii) synaptical plasticity and (iii) structural plasticity. These processes have different time scales namely, spikes – milliseconds, synaptical plasticity – hours, structural plasticity – days. In the present paper we take into account the first and third levels of consideration. In the future we plan to include in our model the second level.

In this paper we present a mathematical model of the neural activity, underlying the development of neural networks. The basis of our diffusion model is the experimental support of physiological and anatomical data. Numerical simulations show the neural network growth, and how neural activity controls this process. The results may be used for experimental verification of the neural network growth and for conditions of new experiments. Some parameters of our model have no experimental basis (e.g. dependence of amount of AGM released by neurons on activity) and may need to be verified in future experiments.

Models of axon guidance have been considered in detail by Hentschel and van Ooyen [9]. Three types of diffusible molecules have been considered: a chemoattractant released by target cells, a chemoattractant released by the axonal growth cones and chemorepellant released by axonal growth cones. Two cases were considered namely, (i) diffusible signals only, and (ii) contact interactions with diffusible signals. It was shown that target-derived chemoattractant controls axon guidance, the axon-derived chemoattractant and chemorepellant control bundling and debundling. The dynamics of chemicals concentrations are described by standard diffusion equation. Every chemical has its own diffusion constant, the release rate and degradation parameter. The release rate constants of chemicals has no dependence on the state of the cell which releases them. In the framework of the model the growth cones response to the concentration gradients of chemicals and total response of the growth cone are the result of two attractive and one repulsive concentration gradient.

Our model, in the part concerning AGM's diffusion and growth cone movement, is based on the above mentioned models. For simplicity we consider only one type of chemoattractant. For description of the movement of growth cone one uses more complicated equations. The main difference is that, the release of chemoattractant is controlled by activity of the target cells, and the growth rate of the growth cones depends on the activity state of the neuron with growing axon. Our model can be considered as generalization in the point of neuron activity, of the model presented in the [9].

Some models of activity-dependent neural network development have already been considered. First of all the model suggested by van Ooyen and collaborators [10, 11]. The model consists of initially disconnected neurons, modeled as neuritic field, which are organized into a network under influence of their internal activity. The growth of neurites are connected with Ca^{2+} concentration inside the cell. Therefore, the growth of neurites depends on their own level of activity, and the neurons become connected when their fields overlap. According to this model the high level of activity causes neurites to retract, whereas low level allows further outgrowth. From mathematical point of view they used a system of coupled differential equations for neural activity and connection strength. They showed, that spatial distribution of the cells can create connectivity patterns in which hysteresis appears and complex periodic behavior takes place [10, 11].

The Segev with collaborators presented a model that incorporates stationary units representing the cells soma and communicating walkers representing the growth cones. The dynamics of the walker's internal energy is controlled by the soma, and they migrate in response to chemorepulsive and chemoattractive glues emitted by the soma and communicate with each other and with the soma by means of chemotactic feedback [12].

Our model is based on axon guidance by extracellular signals released by other neurons. Our consideration is based on the diffusion of the AGM. We already considered this approach before in simple form [13] with binary neurons and without detail consideration of the process of diffusion. Also, the parameters of the model have had no connection with reality and were taken from the mathematical point of view to obtain suitable results. The main novelty in our approach is that we consider the activity-dependence of the processes underlying neural network growth in more detail.

II. NEUROBIOLOGICAL MOTIVATION

A. Axon growth and guidance

Axon growth requires the interplay of many processes: producing cytoplasmic and membrane elements, shipping these building blocks to the right compartment and inserting them into the growing axon and coordination of all these processes.

The tips of growing axons equipped by a very specialized structure, called growth cone, which is specialized for generation forward tension on the elongating axon. Growth cone's cytoskeleton consist of microtubules mostly located in central domain of the growth cone (lamellipodia), and actin filaments located in the lamellipodia and finger-like structures (filopodia). Actin monomers in the peripheral domain undergo constitutive filament assembly, elongating

the lamellipodia and filopodia and pushing the growth cone membrane in forward direction. Simultaneously actin filaments are dragged back motors into central domain by myosin-like motors where the actin filaments depolymerize. The advance of peripheral domain of the cone determined by the balance of anterograde polymerization and retrograde retraction of actin. If the balance is shifted toward forward protrusion, the decrease of in retrograde flow of actin filaments is accompanied by microtubule polymerization into the peripheral domain, moving the central domain of the growth cone forward and elongating the axon [14].

A great variety of extracellular signals have been found to regulate axon growth [15]. Extracellular guidance signals can either attract or repel growth cones, and can operate either at close range or over a distance. In the literature a family of chemicals has been found, which in mammals include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins, netrins, slits, semaphorins, ephrins [14, 16]. Diffusible cues are netrins, neurotrophins, NGF, BDNF among others. The neuronal growth cone uses surface receptors to sense these cues and to transduce guidance information to cellular machinery that mediates growth and turning responses. These guidance factors we will call axon guidance molecules (AGM).

Recent studies have shown that electrical activity is required for growing axons to reach their appropriate target area [17, 18]. In neurons in culture, the changes in growth cone motility after electrical stimulation are accompanied by an influx of calcium through voltage-sensitive calcium channels. The effects of electrical activity and increases in intracellular calcium concentration on growth cone morphology are not the same for all neurons. Some growth cones collapse, some show greater motility and others do not respond at all, depending on the type of neuron, the type of neurite (axon versus dendrite) and environmental factors [19]. It has been found that there are several different signals and signal transduction mechanisms that ultimately result in alterations of the cytoskeletal structure and growth cone motility. Modern experimental investigations show that essential role in controlling growth cone guidance are Ca^{2+} signals. The Ca^{2+} concentration in growth cones is controlled by various channels, pumps and buffers. Guidance cues causes the opening of plasma membrane calcium channels. One of the best studied plasma membrane channel types on growth cones is voltage-operated calcium channels. Guidance of axons to their targets probably involves at least three Ca^{2+} – dependent effects on motility in particular, growth promotion, growth inhibition or collapse, and directional steering (turning). Global Ca^{2+} signals can regulate membrane dynamics and cytoskeletal elements to control elongation, whereas localized Ca^{2+} signals can cause asymmetric activation of downstream effector proteins to steer the growth cone. A small Ca^{2+} gradient produced by modest Ca^{2+} influx or release induces repulsion, whereas a larger Ca^{2+} gradient produced by greater Ca^{2+} influx in combination with release induces attractive turning [20]. A set of experimental results leads to "Ca²⁺ set-point" hypothesis: normal growth cone motility depends on an optimal range of $[\text{Ca}^{2+}]$ and neurite growth stops above or below this optimal range [21]. Therefore, Ca^{2+} regulation of growth cone motility depends on both the spatio-temporal patterns of Ca^{2+} signals and the internal state of the neuron, which is modulated by other signals received by the neuron. Thus, a rise in $[\text{Ca}^{2+}]$ in the growth cone activates numerous target proteins (CaM, CaMKII, myosin, calpain, calcineurin etc.) and cellular machinery which regulates actin and microtubule dynamics to provide the growth cone extension and steering [8].

B. Synaptogenesis

When a growth cone guided by AGM reaches an appropriate target cell, the synaptogenesis and synapse refinement processes start. Synapse formation is controlled by dynamic interactions between various genes and their encoded proteins and occurs throughout development to generate synapse specificity [22, 23]. The modern version of Dale's principle suggests that all of a particular neuron's terminals release the same set of neurotransmitters [24]. Nevertheless, it is well known that a neuron can store and presumably release the different sets of transmitters from individual axon endings [25]. The neurotransmitter choice of the neurons depends on programmed and environmental factors, and this process is neither limited by a critical period nor restricted by their insertion in a network [26]. Calcium transient patterns plays a key role in the differentiation of neural precursor cells, and their frequency may specify neuronal morphology and acquisition of neurotransmitter phenotype [27]. Neuronal activity also plays a main role in the neuronal connection establishment [28]- [30] and refinement [31] processes. The electrical activity of neurons can regulate the choice of neurotransmitter in cultured neurons through calcium influx and can differentially affect the regulation of transmitter expression [32]. Certain neurons choose the neurotransmitter which they use in an activity-dependent manner, and different trophic factors are involved in this phenotype differentiation during development. Regulation of transmitter expression occurs in a homeostatic manner. Suppression of activity leads to an increased number of neurons expressing excitatory transmitters and a decrease number of neurons expressing inhibitory transmitters and vice versa [33]. Based on the above discussion we assume that each neuron's axon can release different neurotransmitters and can establish different types of synaptic connections (inhibitory or excitatory). The type of synapse can be determined by state of presynaptic or/and postsynaptic neuron. For simplification we assumed that the type of a synaptic connection between cells depends on the state of postsynaptic cell at synaptogenesis process.

C. Activity dependent AGM release

Release of some neurotrophic factors can be triggered by external stimulation and neuron's electrical activity [34, 35]. The activity dependent release of AGM's is a key assumption in our model. We doubt there is complete proof of activity dependent AGM's release and we consider this point an hypothesis.

III. THE MODEL

Let us proceed to description of the model adopted here. The concentration of AGM, $c_i = c_i(\mathbf{r} - \mathbf{r}_i, t)$, at point \mathbf{r} in the moment t released by the i -th neuron at point \mathbf{r}_i can be found as the solution of the equation

$$\frac{\partial c_i}{\partial t} - D^2 \Delta c_i + k c_i = J_i(\mathbf{r}, t). \quad (1)$$

Here, D^2 and k are AGM diffusion and degradation coefficients in the intracellular medium respectively. The source J_i is amount of the AGM per unit time. It is well-known that the solution of this equation has the following form

$$c_i(\mathbf{r} - \mathbf{r}_i, t) = \int G_d(\mathbf{r} - \mathbf{r}', t) c_i^0(\mathbf{r}') d\mathbf{r}' + \int_0^t dt' \int G_d(\mathbf{r} - \mathbf{r}', t - t') J_i(\mathbf{r}', t') d\mathbf{r}', \quad (2)$$

where $c_i^0(\mathbf{r})$ is initial distribution of the concentration, d is dimension of the problem and the the Green function has standard Gaussian form

$$G_d(\mathbf{r}, t) = \frac{1}{(4\pi t D^2)^{d/2}} e^{-kt - \frac{\mathbf{r}^2}{4t D^2}}. \quad (3)$$

We suppose that in the initial time there is no AGM and the process is managed by the source

$$J_i(\mathbf{r}, t) = a \delta^{(d)}(\mathbf{r} - \mathbf{r}_i) j_i(t), \quad (4)$$

which is concentrated at the i -th neuron. The parameter a describes amount of AGM released per unit second. This quantity means the amount of AGM per unit time. The $j_i(t)$ describes activity of the neuron and $j_i(t) \leq 1$.

Using this information we have the following form of the concentration

$$c_i(\mathbf{r} - \mathbf{r}_i, t) = a \int_0^t dt' G_d(\mathbf{r} - \mathbf{r}_i, t - t') j_i(t'). \quad (5)$$

For description of neural electrical activity several models have been developed [36]. For simplicity we take the activity $j_i(t)$ is the subject for the equation [37]

$$\tau \frac{dj_i(t)}{dt} = -j_i(t) + f \left(j_i^{ext}(t) + \sum_{k=1, k \neq i}^N \omega_{ik} j_k(t) \right), \quad (6)$$

where the functional f has step form

$$f(x) = x \theta(x), \quad (7)$$

with step function θ and N is amount of neurons. The matrix Ω with elements ω_{ik} describes the influence the k -th neuron to i -th neuron; $\omega_{ik} = 1$ means excitatory and $\omega_{ik} = -1$ inhibitory connections, for $\omega_{ik} = 0$ there is no influence. The functions $j_i^{ext}(t)$ describe the external sources which excites i -th neuron. Now we define the vector $\mathbf{g}_i(t)$ which describes the tip of the axon which started to grow from i -th neuron. It is subject for equation

$$\frac{d\mathbf{g}_i}{dt} = \lambda \mathcal{F}(j_i) \sum_{k=1}^N \nabla c_k(\mathbf{g}_i - \mathbf{r}_k, t), \quad (8)$$

where functional \mathcal{F} has the form of the step function, too:

$$\mathcal{F}(j) = \theta(j^{th} - j). \quad (9)$$

The functional \mathcal{F} , in fact, is smooth function of activity j . In our model we adopt the simplest form of this functional as a step-function by using the threshold parameter. It means that the axon is quiescent if the activity of its neuron is greater then some threshold value j^{th} . The parameter λ is a coefficient describing axon's sensitivity and motility.

At the initial moment we set matrix $\Omega = 0$ which means no connections between neurons. Then we solve the above equations (8), (6), (5) assuming that some neurons are excited by external force that is assuming that some of $j_i^{ext}(t)$ are not zero. We obtain position \mathbf{g}_i of the axon's tip at the moment t . If i -th axon makes connection with k -th neuron we set $\omega_{ik} = \pm 1$.

IV. RESULTS

In this section we present the result of the numerical simulation of the model considered above. We simulate two ($N = 9$ neurons) and three ($N = 27$ neurons) dimensional realizations of the model. For simplicity we consider the network of neurons in form of the lattice with increment (distance between neurons) $d = 0.5 \text{ mm}$. Each neuron has single growth cone, which we consider as its axon. Initially all growth cones are located near its soma, and all synaptic weights are equal to zero ($w_{ik} = 0 \text{ } i, j = 1 \dots N$), which means no connections between neurons. The system of differential equations (8), (6), (5) were integrated simultaneously by the Euler method. The parameters used in the model were taken from different experimental findings and we list them below.

1. The AGM diffusion coefficient $D^2 = 6 \cdot 10^{-7} \text{ cm}^2/\text{s}$, [38].
2. The amount of AGM per unit second $a = 10^{-5} \text{ nM/s}$, [38, 39].
3. The relaxation time of activity $\tau = 10 \text{ ms}$, [37].
4. The coefficient describing axon's sensitivity and motility $\lambda = 4 \cdot 10^{-6} \text{ cm}^2/\text{nM} \cdot \text{s}$, [40].

The threshold parameter j^{th} is a parameter exclusive to our model and for this reason there is no experimental value that can be assumed to it. We set the threshold parameter, $j^{th} = 0.51$, to take good agreement with experimental observation of the network growth [5]. The degradation coefficient k may be found, in principal, from specific experiments. Unfortunately, there is no information about this parameter and we put $k = 10^{-3} \text{ s}^{-1}$ to be in agreement with network growth. This parameter regulates the rate of the axon's growth. The greater k the smaller rate of axon's growth.

There is another threshold parameter of activity which defines sort of connections: $\omega = +1$ or $\omega = -1$. For homeostasis we take this parameter to equal 0.51. If activity of postsynaptic neuron's greater then 0.51 we set $\omega = -1$ and vice versa. This is a crude approximation but it is enough to describe the neurons networks development.

As an example we present in Fig. 1 and 2 the neural network which was obtained by using the following training pattern sequence. (We show snapshots of the dynamic process; full animation may be found in URL: <http://neurowiring.narod.ru/video.html>)

A. 2 dimensional case

Neuron A was being active with activity 1 during the time period from 0s to 800s and activity of other neurons in this period is zero. In Fig. 1a we show the snapshot of the system at the moment $t = 791\text{s}$. We observe that the nearest two neurons growth cones grow to this active neuron A. After some time the growth cones reached the active neuron A and synaptical connects appear $w_{1,2} = 1, w_{1,4} = 1$. The growth cones of the distant neurons do not appear because concentration of the AGM far from the active neuron is negligible.

In the interval $t = 800\text{s} - 1200\text{s}$ the central neuron was active with activity 1. The neuron B was active in interval $t = 1200\text{s} - 3500\text{s}$. In Fig. 1b we reproduce the snapshot of the system at the moment 2701s. We note that the growth cones of neurons close to the another neuron did not reach this central neuron and the neuron B became active. The consequence of this fact is curved form of the axons.

Since the moment $t = 3500\text{s}$ the neuron C plays the role due to its activity (see Fig. 1c and 1d). We show the snapshots of the system at the moments 3501s and 9001s. We observe the the new connections to neuron B appeared $w_{3,5} = -1, w_{3,6} = -1$. The growth cones which did not reach neuron B turned to the active neuron C. The growth cone of the active neuron C which started to grow in the earliest moment is quiescent in the period of its activity (see Fig. 1c and 1d). Mathematically it is described by threshold function \mathcal{F} (9).

We observe that the topology of the neural network strongly depends on the sequence of neuronal activity the reason of which is external influence. In real system the growth of the connections in the complex connection structure will depend on the internal oscillation of activity rather then external signals. The external influence is very important at the initial time during the network development.

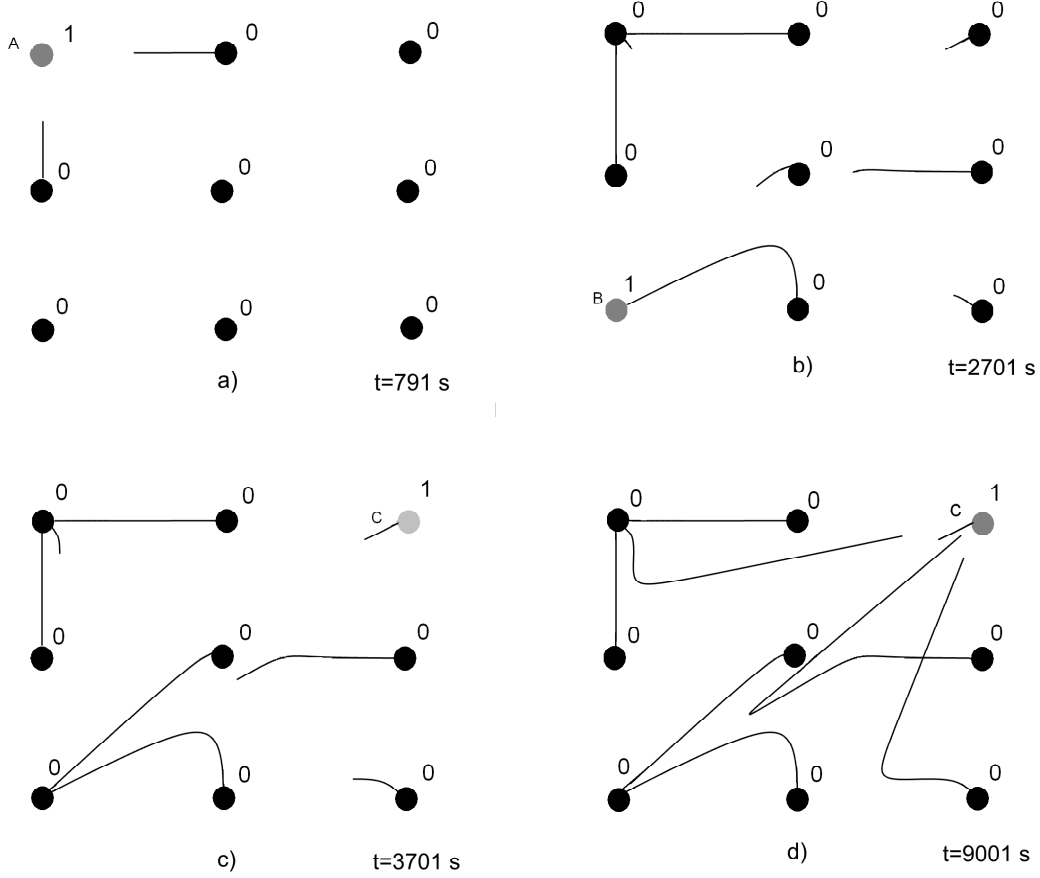


FIG. 1: The numerical simulation the development of the two-dimensional neuron's network. The neurons are shown as circles. The blackness of the circles proportional to activity: zero activity plotted by black and maximal activity is grey. The number close to neurons means activity of them. The black lines are axons. We show snapshots of neuron network for different moments of time namely, $t = 791s, 2701s, 3701s, 9001s$.

V. 3 DIMENSIONAL CASE

The situation in this case is close to the 2 dimensional case. The first neuron in the upper cone was active in the period $t = 0s - 2000s$ with activity 0.8. In the period $t = 2000s - 4000s$ the neuron A was active. The snapshot for moment $2500s$ is shown in Fig. 2a. In the period $t = 4000s - 6000s$ the neuron B was active (see Fig. 2b for $t = 4900s$). The neuron C was active in the period $t = 6000s - 9000s$ (see Fig. 2c for $t = 8000s$). The neuron D starts to be active since moment $9000s$ (see Fig. 2d for $t = 17000s$).

We observe the network development close to 2 dimensional case. The topology of the network depends on the sequence of neuronal activity.

VI. DISCUSION

In above sections we developed the new theoretical approach to describe the growth of the network of neurons. The model is based on the diffusion of the AGM and dynamic of the diffusion satisfies to diffusion equation. The rate of the growth cone movement is proportional to concentration gradient which should be the case. The peculiarity of the model is that the activity of the neuron manages the release of the AGM which influence to axon's growth. This process leads to appearance of the new connections in the system and network development. In framework of the model and with real parameters obtained in experiments we have correct picture of network growth (see Fig. 1 and

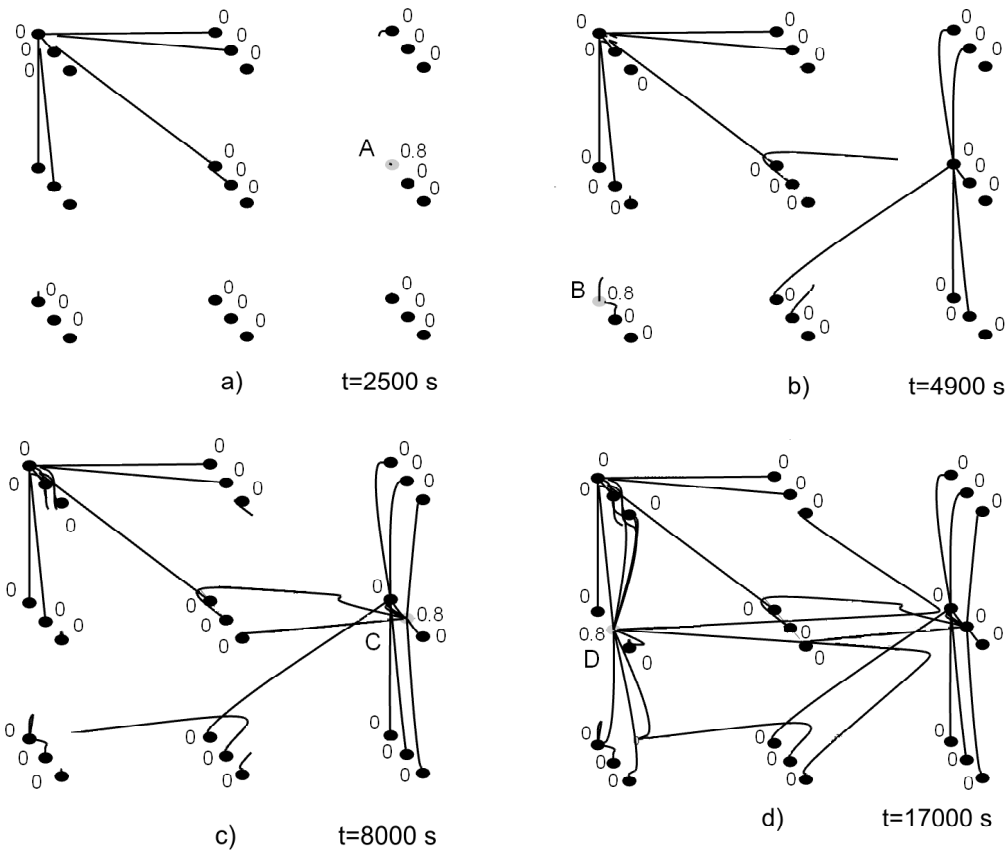


FIG. 2: The numerical simulation the development of the three-dimensional neuron's network. The neurons are shown as balls. The blackness of the balls proportional to their activity: zero activity plotted by black and maximal activity is grey. The number close to neurons means activity of them. The black lines are axons. We show snapshots of neuron network for different moments of time namely, $t = 2500s, 4900s, 8000s, 17000s$.

2) in temporal scale. In particular, the Fig. 2 ($t = 17000s$), shows some neurons to have only long-range connections without any local connections. This shows how nested neural networks are formed in the cerebral cortex.

Our expectations of the network topology and direction of the axon's growth were realized in framework of the model. We confine ourselves for two reasons. First of all we would like to consider in detail the dynamics of the axon's growth in dependence of the neurons activity. Second, the real system contains huge amount the neurons. The present calculations are confined by power of our computers. In the future we intend to make numerical simulations for more real amount of the neurons and axons.

Real cortical networks have more complex structure comparing with that obtained in framework of our model. The neural network development is controlled by many factors which are out of scope of our model, namely, cell adhesion molecules, multiple guidance factors and etc. In the model presented here we considered only one of them, the axon guidance by single diffusable factor, which is, in fact, the most important factor in activity dependent development. In our model axons have only one branch and single growth cone, without taking into account axon branching. The cortical neuron's axons have plenty branched structure and different branches of single axon grow to different target neurons. In the model each neuron can make connection only with one target neuron. Alongside with guidance growth cone by chemoattraction the process is controlled also by chemorepellants. Different types of neurons have different properties and cortex consists of a lot amount of different neurons. In the model presented here we take into account only one type of the neurons. The guidance of particular growth cones to the target is not controlled by single AGM. In particular parts of growth cone trajectory the different AGM's take part in axon guidance. The growth cones can go to long distances and they result to long-range intra-cortical and cortico-cortical connections.

Real neurons possess also the strong branched dendrite structure. The dendrite growth represents very complex process which is managed by many factors. In our model the axons' growth cones make synaptic connections directly to a soma. The most of synaptic connections in cortex are on dendrites which are absent in our model. To obtain a

more precise picture of cortex development we should take into account also the morphological properties of neurons. We plan to include dendrites and morphological properties of neurons into our model in future investigations.

VII. CONCLUSIONS

The theoretical framework developed here can be used for description the development of a particular set of neurons constituting the neural system. In this paper we show that chemotactically guidance of growth cones by AGM released by neurons can be a basis of neural networks growth, topology and development. The concentration of AGM released by individual cells is basis for correct axon guidance with appropriate rate. All parameters describing the model are taken from different real experiments. This model can be used for description the growth of developing neural network. It is well known that the wiring of neural networks takes place on the chemotaxis based axon guidance. The connections structure between neurons is very complex in real networks. Such complex structure can appear only by switching of and switching of the chemical signal that regulates the growth of axon. Using this model we conclude that these process can be based for learning, because creation of new connection leads to increasing of network complexity in structure. Another application of this model is in treatment of damaged neural tissue by stem cells. Using this model we may describe the processes of integration of stem cells into existing network. This model can be used also for understanding the processes which takes place at deep brain stimulation by electrical current. We showed that the electrical stimulation of individual cells leads to alternation of AGM release and in growth cones guidance, and deep brain stimulation can change the network structure. Another application of our model can be in modeling of imprinting memories in cultured neural networks [41].

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